REMARKS

Claims 1, 3-10, 12, 35-37, and 39-46, 49, and 51 are pending in the present application. Independent claims 1 and 43 have been amended by incorporating the subject matter of claim 2 therein. Claim 43 has further been amended to recite an oral tablet pharmaceutical composition, which is supported by, *inter alia*, the abstract of the instant application at line 1. Claims 2, 47, and 48 have now been cancelled and claims 49 and 51 have been appropriately amended; e.g., changing dependency, etc., to be consistent therewith. Accordingly, no new matter has been introduced into the application by the above-amendment.

Interview Summary

Applicants wish to express their appreciation to Examiner Kishore for the courtesies extended to applicants' undersigned representative during the personal interview of November 3, 2004. During the interview, applicants pointed out that the double patenting rejections over US 6,680,334 were without merit as neither the inventors nor the assignee are in common with the present application. The question of whether an interference should be sought was discussed. The Examiner advised that he would not initiate an interference from his side, but if applicants desired the USPTO to consider declaring an interference, the applicants should file a formal request.

The Examiner thought that incorporating claim 2 into claim 1 was very likely to make claim 1 allowable. However, the Examiner thought that claims 43 and 52 were not patentable over the McDaid and Deasy article. Since these claims substantially correspond to claims 3 and 1, respectively, of US 6,680,334, it was suggested that the subject matter of claims 43 and 52 be sought, if at all, in a divisional application and the

interference, if desired, pursued/requested therein. In this way, the allowance of the present application may be expedited.

Finally, the restriction requirement was discussed. The Examiner suggested that a request for rejoinder would be viewed more favorably if the main independent claim was allowable.

Restriction Requirement

Claims 44-46 and 51 have been withdrawn from consideration because they relate to the presence of two active ingredients. Applicants traverse this restriction as these dependent claims are not "independent and distinct" inventions as defined in 35 U.S.C. § 121 or MPEP § 800. Rejoinder of these claims is requested, especially in view of the current amendment to claim 43, which is believed to make the claims clearly patentable. Since claim 43 is allowable, dependent claims 44-46 and 51 are likewise allowable. Reconsideration and rejoinder of these claims are respectfully requested.

Rejection under § 112

Claim 48 has been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. This rejection is respectfully traversed.

While not conceding the propriety of the Examiner's position, claim 48 has been cancelled by the above-amendment thereby rendering this rejection moot. Accordingly, withdrawal of this rejection is requested.

Double Patenting Rejections

Claims 1-10, 12, 35-37, 39-43, and 47-49 have been rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-3 of U.S. 6,680,334, as allegedly providing an improper timewise extension of the existing patent rights.

Further, claim 52 has been rejected under 35 U.S.C. § 101 as claiming the same invention as claimed in US 5,680,334. These rejections are respectfully traversed.

The present application can not be rejected for double patenting over U.S. 6,680,334 because Patent No. 6,680,334 is not the inventors' patent nor is it commonly owned with the present application. That is, no inventors are in common; and the present application is owned by Synthon BV while the US 6,680,334, according to the face thereof, is owned by Pfizer, Inc. In any event, the US 6,680,334 is not owned by Synthon BV. In the absence of evidence of common inventorship or ownership, the Examiner lacks the factual foundation to make a double patenting rejection over U.S. 6,680,334. Therefore, reconsideration and withdrawal of these rejections are respectfully requested.

Rejection over Young under § 102

Claims 1, 2, 7-10, 12, 43, 47-49, and 52 have been rejected under 35 U.S.C. § 102(c) as allegedly being anticipated by Young, U.S. 6,057,344. This rejection is respectfully traversed.

The Examiner's rejection is based on a miss-reading of Young. Specifically, contrary to the Examiner's position, Young does not teach the crystallization of amlodipine free base. Rather column 10, lines 1-5 refer to the crystallization of a cinchonidine salt of an azido-acid precursor of amlodipine (see reaction scheme in column 9). A diastereomerically pure cinchonidine salt is crystallized out of solution to effect separation of the optical isomers. This optically pure salt is subsequently esterified and the azido group reduced to an amino group to form optically pure amlodipine free base. But even then, the optically purified amlodipine free base is not taught to be crystallized. Instead, Young teaches that the produced amlodipine "is most conveniently

isolated as the salt of an acid, e.g. as the maleate 5." (See Young, col. 10, lines17-18). Thus, Young teaches away from attempting to precipitate, i.e., "isolate," the amine base (amlodipine) in favor of the precipitation of an amlodipine salt.

Similarly, Young column 10 line 65 also fails to teach or suggest crystallizing amlodipine free base or using the same. Rather, this passage indicates that amlodipine can be converted to a salt. Nothing suggests crystallizing the amlodipine free base. Given the earlier disclosure in lines 17-18, the reader is lead to use one of the acid salts described in line 65 *et seq.*, to isolate the optically purified amlodipine as a salt from the reaction mixture.

Likewise, Examples 4 and 8 both fail to teach the use of applicants' claimed crystalline amlodipine free base. Example 4 uses an injectable amlodipine in a solvent vehicle. Example 8 shows a recipe for tablets but fails to state if crystalline amlodipine free base is used. Indeed, given that Example 8 refers to "active ingredient, (-) amlodipine" it is unclear if the base *per se* is recited or if it is a general reference to the amount of active ingredient, such as (-) amlodipine maleate, expressed in terms of the free base, as is commonly done with pharmaceutical formulations. In any event, neither Example teaches crystalline amlodipine free base, much less how to obtain the same.

Accordingly, the Examiner's basic premise regarding Young is incorrect. Failing to teach the formation or use of crystalline amlodipine free base, Young fails to identically describe the presently claimed invention. Furthermore, nothing in Young teaches an amlodipine free base tablet having the claimed low punch residue. Therefore, the presently claimed subject matter is not anticipated and reconsideration and withdrawal of this rejection are respectfully requested.

Rejection over Young under § 103

Claims 1-10, 12, 35-43 and 47-49 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Young. This rejection is respectfully traversed.

As explained above, Young fails to teach crystalline amlodipine free base. Additionally, Young fails to teach or suggest a crystalline amlodipine base-containing tablet having low punch residue as per claims 1 and 43. Indeed, such a result is not expected given the teachings in the art of the difficulties with tabletting amlodipine free base. As explained in Davison, Table 2, amlodipine free base exhibited a stickiness of 2.02 [μ]g amlodipine.cm^{-2}.$tablet^{-1}$ while amlodipine besylate had approximately half of the stickiness at a measured residue value of 1.17 [μ]g amlodipine.cm^{-2}.$tablet^{-1}$. But as shown in Example 9 of the present specification, crystalline amlodipine free base tablets can have an even lower stickiness than amlodipine besylate. Specifically, in Example 9 the crystalline amlodipine free base achieved a residue of only 0.66 μg amlodipine/cm^{-2} per tablet while the amlodipine besylate was 1.16 μg amlodipine/cm^{-2} per tablet, a value almost identical to that reported in Davison. Such a result for an amlodipine free base-containing tablet is not suggested by Young. Similarly, the executed Rule 132 Declaration of Arlette Vanderheijden, submitted on April 16, 2004, confirms the unexpected nature of the present invention. In the Declaration crystalline Forms I and III gave the best results and the amorphous amlodipine free base was incapable of being tabletted. Nothing in Young teaches the potential advantages of crystalline amlodipine free base, nor that amlodipine free base tablets can be made with low punch residue as claimed.

In the absence of any teaching in Young of using crystalline amlodipine free base in a tablet composition and in the absence of a reasonable expectation of successfully forming such a tablet with an average punch residue of 0.7 $\mu g \cdot cm^{-2}$ per tablet or less, the presently claimed subject matter could not have been obvious to the worker of ordinary skill in the art at the time the invention was made. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Rejection over Lazar and Davison

Claims 1-10, 12, and 35-43 and 47-49 have been rejected under 35 U.S.C. § 103(a) over U.S. patent 5,155,120 (Lazar) in combination with U.S. patent 4,879,303 (Davison). This rejection is respectfully traversed.

Neither Lazar nor Davison teach a pharmaceutical tablet containing crystalline amlodipine free base and having an average punch residue of 0.7 $\mu g\ cm^{-2}$ per tablet or less as claimed in claims 1 and 43 of the present application. Lazar teaches a new use for amlodipine, but instead of using amlodipine free base, all of the examples in Lazar use amlodipine besylate (see Lazar col. 3 lines 29-31). On the other hand, Davison teaches a tablet with amlodipine free base, but teaches that such a tablet has a punch residue of 2.02 $\mu g\ cm^{-2}$ per tablet. Such a disclosure hardly suggests the formation of an amlodipine free base tablet having a punch residue of 0.7 $\mu g\ cm^{-2}$ or less; i.e., about one third or less the punch residue in Davison and less than Davison's preferred amlodipine besylate. And Davison is silent as to the amlodipine free base being in crystalline form. Subsequent patents indicate that in fact the Amlodipine free base product in Davison was not crystalline (See U.S. 6,680,334). From the Lazar and Davison disclosures the worker of ordinary skill is not led to form the presently claimed invention. In fact, the worker of

ordinary skill in the art would not have a reasonable expectation of success in forming the claimed tablets having low punch residue. Absent improper hindsight reconstruction, there is no motivation or suggestion of the presently claimed subject matter in the combination of Lazar and Davison.

Furthermore, the Examiner's criticisms of the Rule 132 Declaration of Arlette Vanderheijden are unfounded. Firstly, the executed Declaration was filed April 16, 2004 and appears in the IFW on that date as "Oath or Declaration filed." Thus the Examiner's argument in July 2004 that the Declaration is unsigned is in error. Secondly, the fact that the Declaration compared a single formulation does not render it unpersuasive. Previously the Examiner requested a comparison to show that the different forms of amlodipine free base could make a difference in pharmaceutical composition performance. The Declaration does this and in particular shows the superiority of crystalline amlodipine free base over amorphous amlodipine free base. Moreover, the Declaration evidence is in addition to Example 9 of the present specification where another formulation using crystalline Form I amlodipine free base also exhibits low punch residue. The aggregate of this date overcomes any *prima facie* case of obviousness.

Nonetheless, in order to remove the Examiner's criticisms, claims 1 and 43 have been amended to recite a low punch residue. Tablets that do not achieve the claimed average residue of amlodipine on the tablet punch of 0.7 $\mu g \cdot cm^{-2}$ per tablet or less are not within the scope of the claims. Thus, only tablets exhibiting the claimed unexpectedly superior (e.g. low) punch residue are within the scope of the claims. Since nothing in Lazar or Davison teaches such a tablet, the presently claimed subject matter is clearly

unobvious. Thus, the claimed invention is unobvious within the meaning of 35 U.S.C. § 103.

In view of the above amendments, the data of record, and the failures and gaps in the teachings in Lazar and Davison vis-à-vis the present invention, the presently claimed subject matter is novel and unobvious over the applied prior art. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection over Lazar and Young

Claims 1-10, 12, and 35-43 and 47-49 and 52 have been rejected under 35 U.S.C. § 103(a) over Lazar in combination with Young. This rejection is respectfully traversed.

The Examiner alleges that Lazar lacks only a teaching of microcrystalline cellulose and other excipients to make the claimed invention as recited in several of the dependent claims. Young is applied as providing these deficiencies. This position is in error.

Contrary to the Examiner's position, Lazar also fails to teach or suggest crystalline amlodipine free base, for the reasons set forth above. Additionally, Lazar fails to teach or suggest an amlodipine free base tablet having a low punch residue as claimed in claims 1 and 43. Young does not overcome these deficiencies for the reasons set forth above. Accordingly, the instant rejection fails to establish a *prima facie* case of obviousness. Therefore, reconsideration and withdrawal of this rejection are requested.

Miscellaneous

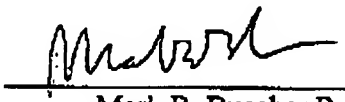
Pursuant to the Examiner's requests during the personal interview, applicants are submitting herewith a copy of the Examiner initialed PTO-1449 form and another copy of the McDaid and Deasy article.

Conclusion

In view of the above amendments and remarks, all claims pending in the present application define novel, patentable subject matter. Reconsideration of the rejections and allowance of the application are respectfully requested.

Should the Examiner have any questions regarding this application, he is encouraged to contact Mark R. Buscher (Reg. No. 35,006) at telephone No. 703 753 5256.

Respectfully submitted,



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